Still too little, too late? Ten years of growth hormone therapy baseline data from the NordiNet® International Outcome Study

Polak, Michel ; Konrad, Daniel ; Tønnes Pedersen, Birgitte ; Puras, Gediminas ; Šnajderová, Marta

Abstract: BACKGROUND We investigated time trends in age, gender, growth hormone (GH) dose and height standard deviation score (SDS) in children with GH deficiency (GHD), born small for gestational age (SGA) or with Turner syndrome (TS) starting GH treatment. METHODS Data were obtained from children enrolled in the NordiNet® International Outcome Study (IOS) between 2006 and 2015 in the Czech Republic, France, Germany, Serbia and Montenegro (all indications), and Switzerland and the UK (GHD only). Trends were analyzed by linear regression. Patients were divided by age into early-, medium- or late-start groups in three different time periods. RESULTS Approximately one-third of children starting treatment for GHD were girls, with no apparent increase in proportion over time. The mean baseline age for starting treatment decreased significantly ($p<0.001$) for both GHD and SGA in the Czech Republic and Germany. In the other countries studied, over 40% of children started treatment for GHD and SGA late (girls >10, boys >11 years) between 2013 and 2015. The mean baseline GH doses were largely within recommended ranges for GHD and SGA, but below the lowest recommended starting dose for TS in almost every year since 2011 except in France. CONCLUSIONS Approximately one-third of children starting treatment for GHD were girls. Between 2013 and 2015, more than 40% of children started treatment for GHD and SGA late except in Germany and the Czech Republic. TS patients received below-recommended doses. These results highlight the need for earlier identification of short stature in children, particularly girls, and for dose optimization in TS.

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Methods: Data were obtained from children enrolled in the NordiNet® International Outcome Study (IOS) between 2006 and 2015 in the Czech Republic, France, Germany, Serbia and Montenegro (all indications), and Switzerland and the UK (GHD only). Trends were analyzed by linear regression. Patients were divided by age into early-, medium- or late-start groups in three different time periods.
Results: Approximately one-third of children starting treatment for GHD were girls, with no apparent increase in proportion over time. The mean baseline age for starting treatment decreased significantly ($p < 0.001$) for both GHD and SGA in the Czech Republic and Germany. In the other countries studied, over 40% of children started treatment for GHD and SGA late (girls >10, boys >11 years) between 2013 and 2015. The mean baseline GH doses were largely within recommended ranges for GHD and SGA, but below the lowest recommended starting dose for TS in almost every year since 2011 except in France.
Conclusions: Approximately one-third of children starting treatment for GHD were girls. Between 2013 and 2015, more than 40% of children started treatment for GHD and SGA late except in Germany and the Czech Republic. TS patients received below-recommended doses. These results highlight the need for earlier identification of short stature in children, particularly girls, and for dose optimization in TS.

Keywords: growth hormone; growth hormone deficiency; NordiNet® International Outcome Study; small for gestational age; Turner syndrome.

Introduction

A number of studies have reported on factors associated with response to growth hormone (GH) therapy for different indications. In GH deficiency (GHD), age at GH treatment start and height deficit at baseline are inversely associated, whereas GH dose is positively associated, with the response [1–3]. Age at treatment start and GH dose were also shown to be similarly associated with growth response in children born small for gestational age (SGA) without postnatal catch-up growth [1, 4, 5] and in Turner syndrome (TS) [1, 6, 7]. In light of this evidence, it is of interest to investigate real-life baseline characteristics of children starting treatment with GH, as recorded in databases such as the NordiNet® International Outcome Study (IOS) and the Pfizer International Growth Study (KIGS®), and to examine whether clinical practice has changed over time.

The objectives of the current study were to analyze data from NordiNet® IOS to evaluate trends over 10 years (2006–2015) in the age and height standard deviation score (SDS) at which children start GH treatment for GHD, SGA and TS; to investigate whether adequate baseline doses of GH were prescribed over this period; and to identify the proportion of girls treated among patients with GHD and born SGA. As such, the current analysis aims to support and provide additional evidence on aspects different to those reported in two recent studies [8, 9].

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Materials and methods

NordiNet® IOS (ClinicalTrials.gov identifier: NCT00960128) is a non-interventional, multicenter study evaluating the long-term effectiveness and safety of Norditropin® (somatropin; Novo Nordisk A/S, Copenhagen, Denmark) as prescribed by the treating physicians in the real-life clinical setting. NordiNet® IOS was launched in 2006 and data are collected from 23 countries [10].

Children (aged <18 years) with isolated GHD, born SGA or with TS enrolled in NordiNet® IOS who started treatment with GH between 1 January 2006 and 31 December 2015 were included in this analysis. Clinical diagnoses were based on the judgment of the treating physician. For GHD, we analyzed only patients with isolated GHD; those with additional pituitary hormone deficiencies were excluded.

In order to draw meaningful conclusions, only countries with a minimum number of enrolled eligible patients were included in the analyses. Following a preliminary feasibility analysis, this was set at 100 patients for GHD and those born SGA, and 50 patients for TS. For GHD, six countries/country groups met this criterion: the Czech Republic, France, Germany, Serbia and Montenegro, Switzerland and the UK. Serbia and Montenegro were grouped together because data from both countries are collected through the same enrolment flow. For SGA and TS, the Czech Republic, France, Germany, and Serbia and Montenegro met the criterion.

NordiNet® IOS is conducted in accordance with the Declaration of Helsinki and Good Pharmacoepidemiology Practice guidelines [11]. All patients, or their guardians in the case of minors, provide written informed consent for data collection, and all data collected within NordiNet® IOS are anonymized. Centers are included in NordiNet® IOS only after approval of the Local Ethics Committee or Institutional Review Board at individual center level, in accordance with country-specific rules.

Descriptive statistics were applied to age at treatment start, baseline dose of GH, and baseline height SDS, and are presented as mean (standard deviation, SD). Gender distribution in patients with GHD and those born SGA was determined for each year from 2006 to 2015 inclusive. Time trends in age at treatment start, baseline dose of GH, and baseline height SDS within each country were analyzed for each parameter by linear regression, including calendar year as explanatory variable in the model. Regression plots were used to illustrate data trends. The distribution of patients by age group at treatment start (early: girls aged <8 years, boys aged <9 years; medium: girls aged 8–10 years, boys aged 9–11 years; and late: girls aged >10 years, boys aged >11 years) in three time periods (2006–2009, 2010–2012 and 2013–2015) was also determined and reported descriptively.

Statistical analysis was performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). Height SDS was calculated using relevant national references [12–16], or, for Serbia and Montenegro, the Centers for Disease Control and Prevention reference [17].

Results

This analysis included 3974 patients with GHD, 1926 born SGA without spontaneous catch-up growth and 428 with TS (Table 1A–C).

Table 1: Number of patients enrolled by country and year for patients with GHD, short patients born SGA and patients with TS.

GH start year	Czech Republic		France		Germany		Serbia and Montenegro		Switzerland		UK	
	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)
(A) Patients with GHD												
2006	3 (16.7)	15 (83.3)	26 (40.0)	39 (60.0)	42 (27.8)	109 (72.2)	11 (52.4)	10 (47.6)	6 (42.9)	8 (57.1)	5 (62.5)	3 (37.5)
2007	9 (30.0)	21 (70.0)	34 (43.0)	45 (57.0)	61 (29.9)	143 (70.1)	10 (31.3)	22 (68.8)	4 (20.0)	16 (80.0)	4 (40.0)	6 (60.0)
2008	7 (25.0)	21 (75.0)	37 (33.6)	73 (66.4)	63 (30.7)	142 (69.3)	11 (29.7)	26 (70.3)	7 (25.0)	21 (75.0)	16 (44.4)	20 (55.6)
2009	7 (22.6)	24 (77.4)	66 (43.7)	85 (56.3)	64 (30.2)	148 (69.8)	13 (39.4)	20 (60.6)	10 (31.3)	22 (68.8)	2 (25.0)	6 (75.0)
2010	13 (32.5)	27 (67.5)	66 (36.1)	117 (63.9)	53 (34.2)	102 (65.8)	11 (44.0)	14 (56.0)	13 (34.2)	25 (65.8)	9 (50.0)	9 (50.0)
2011	18 (31.6)	39 (68.4)	56 (36.6)	97 (63.4)	37 (26.6)	102 (73.4)	7 (28.0)	18 (72.0)	4 (16.0)	21 (84.0)	10 (29.4)	24 (70.6)
2012	14 (48.3)	15 (51.7)	47 (30.9)	105 (69.1)	43 (34.4)	82 (65.6)	15 (35.7)	27 (64.3)	8 (21.6)	29 (78.4)	7 (28.0)	18 (72.0)
2013	16 (38.1)	26 (61.9)	55 (36.2)	97 (63.8)	32 (30.5)	73 (69.5)	18 (25.4)	53 (74.6)	5 (14.3)	30 (85.7)	1 (4.8)	20 (95.2)
2014	21 (38.9)	33 (61.1)	38 (33.3)	76 (66.7)	23 (32.4)	48 (67.6)	15 (34.1)	29 (65.9)	7 (21.9)	25 (78.1)	13 (43.3)	17 (56.7)
2015	14 (23.0)	47 (77.0)	49 (43.4)	64 (56.6)	30 (33.3)	60 (66.7)	17 (27.9)	44 (72.1)	4 (28.6)	10 (71.4)	2 (25.0)	6 (75.0)
All	122 (31.3)	268 (68.7)	474 (37.3)	789 (62.7)	448 (30.7)	1009 (69.3)	128 (32.7)	263 (67.3)	68 (24.7)	207 (75.3)	69 (34.8)	129 (65.2)

Overall total (all countries, all years): 3974

Table 1 (continued)

GH start year	Czech Republic		France		Germany		Serbia and Montenegro	
	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)
(B) Short patients born SGA								
2006	3 (21.4)	11 (78.6)	41 (62.1)	25 (37.9)	49 (38.0)	80 (62.0)	1 (33.3)	2 (66.7)
2007	4 (28.6)	10 (71.4)	36 (54.6)	30 (45.5)	32 (36.0)	57 (64.0)	1 (100.0)	0 (0)
2008	13 (44.8)	16 (55.2)	31 (48.4)	33 (51.6)	32 (41.0)	46 (59.0)	1 (20.0)	4 (80.0)
2009	12 (37.5)	20 (62.5)	46 (47.4)	51 (52.6)	49 (49.5)	50 (50.5)	1 (20.0)	4 (80.0)
2010	18 (62.1)	11 (37.9)	50 (56.2)	39 (43.8)	33 (47.1)	37 (52.9)	7 (63.6)	4 (36.4)
2011	13 (52.0)	12 (48.0)	37 (56.1)	29 (43.9)	30 (41.1)	43 (58.9)	11 (40.7)	16 (59.3)
2012	14 (56.0)	11 (44.0)	33 (51.6)	31 (48.4)	19 (38.8)	30 (61.2)	13 (50.0)	13 (50.0)
2013	14 (45.2)	17 (54.8)	41 (50.6)	40 (49.4)	23 (39.7)	35 (60.3)	14 (31.8)	30 (68.2)
2014	12 (60.0)	8 (40.0)	29 (44.6)	36 (55.4)	16 (53.3)	14 (46.7)	26 (53.1)	23 (46.9)
2015	12 (48.0)	13 (52.0)	42 (55.3)	34 (44.7)	20 (60.6)	13 (39.4)	31 (44.9)	38 (55.1)
All	115 (47.1)	129 (52.9)	386 (52.6)	348 (47.4)	303 (42.8)	405 (57.2)	106 (44.2)	134 (55.8)

Overall total (all countries, all years): 1926

GH start year	Czech Republic n	France n	Germany n	Serbia and Montenegro n
(C) Patients with TS				
2006	4	8	20	12
2007	8	10	16	6
2008	3	14	13	7
2009	8	23	22	3
2010	11	17	18	4
2011	3	17	13	2
2012	8	18	17	5
2013	7	14	11	9
2014	10	10	8	3
2015	8	14	19	5
All	70	145	157	56

Overall total (all countries, all years): 428

GH, growth hormone; GHD, growth hormone deficiency; SGA, small for gestational age; TS, Turner syndrome.

GHD

For all years combined, in each country, approximately one-third of included patients with GHD were female, except in Switzerland, where only 24.7% of patients were female (Table 1A). No clear pattern of change was observed in any country over time.

The mean age at treatment start by year is shown in Table 2A. For all years combined, the mean (SD) age at treatment start ranged from 8.2 (4.1) years (Czech Republic) to 11.2 (3.5) years (Serbia and Montenegro). From 2006 to 2015 the observed mean age at treatment start decreased from 11.4 (3.6) to 7.3 (3.6) years in the Czech Republic, and from 10.0 (3.9) to 7.7 (3.7) years in Germany (Table 2A); the trend of a decrease in age over time was statistically significant for both countries ($p < 0.001$) (Supplemental Figure 1A). Consequently, the proportions of children starting treatment early increased and the proportion starting treatment late decreased over time in these two countries (Figure 1). In the remaining countries, the mean age at treatment start did not show a clear trend (Table 2A, Supplemental Figure 1A), although the proportion of patients starting treatment late appeared to increase over time in France (Figure 1). In France, Serbia and Montenegro, Switzerland, and the UK,

Table 2: Age at treatment start in years, shown as mean (SD) for patients with GHD, short patients born SGA and patients with TS.

GH start year	Czech Republic	France	Germany	Serbia and Montenegro	Switzerland	UK
(A) Patients with GHD						
2006	11.4 (3.6)	9.9 (3.8)	10.0 (3.9)	10.9 (3.5)	9.1 (3.5)	9.6 (3.6)
2007	9.2 (4.1)	8.7 (4.5)	9.5 (4.1)	11.2 (3.6)	11.0 (3.1)	8.6 (5.6)
2008	10.6 (3.7)	9.2 (4.4)	9.3 (3.8)	11.1 (3.5)	7.6 (2.7)	9.1 (5.0)
2009	10.0 (4.5)	9.0 (4.1)	9.5 (3.6)	11.6 (4.2)	9.9 (3.8)	11.5 (3.4)
2010	8.8 (3.9)	9.6 (4.3)	8.5 (3.9)	10.2 (3.3)	9.7 (4.1)	10.0 (4.9)
2011	7.3 (4.0)	9.3 (4.4)	8.2 (3.8)	10.7 (3.5)	9.6 (3.3)	9.2 (5.1)
2012	7.2 (3.9)	9.5 (4.5)	8.5 (4.1)	11.0 (3.3)	10.3 (3.7)	10.7 (4.2)
2013	7.1 (4.0)	10.1 (4.1)	8.3 (4.1)	11.7 (3.4)	10.1 (4.0)	9.7 (3.9)
2014	7.0 (3.9)	10.6 (3.6)	8.6 (3.7)	11.1 (3.7)	9.5 (2.9)	9.5 (3.8)
2015	7.3 (3.6)	9.5 (4.0)	7.7 (3.7)	11.6 (3.1)	10.5 (3.6)	11.6 (4.4)
All	8.2 (4.1)	9.6 (4.2)	9.0 (3.9)	11.2 (3.5)	9.7 (3.6)	9.7 (4.5)

GH start year	Czech Republic	France	Germany	Serbia and Montenegro
(B) Short patients born SGA				
2006	9.3 (3.6)	7.5 (3.2)	7.5 (3.2)	7.1 (2.6)
2007	8.4 (3.2)	8.1 (4.0)	7.5 (3.1)	8.6 [a]
2008	6.5 (2.7)	8.1 (3.2)	8.3 (2.8)	7.6 (3.6)
2009	8.3 (3.9)	8.9 (3.3)	7.6 (2.8)	11.1 (4.0)
2010	6.8 (3.5)	8.5 (3.6)	7.4 (3.0)	8.5 (3.5)
2011	5.7 (3.0)	8.5 (3.8)	6.9 (3.1)	8.7 (4.2)
2012	6.5 (2.7)	9.0 (3.9)	6.2 (2.3)	8.8 (4.2)
2013	5.9 (2.8)	8.4 (3.5)	6.5 (2.5)	9.4 (4.3)
2014	7.4 (3.0)	8.6 (3.8)	6.6 (2.4)	9.1 (3.7)
2015	5.9 (1.7)	9.5 (3.7)	6.1 (2.4)	9.0 (3.5)
All	6.9 (3.2)	8.5 (3.6)	7.3 (2.9)	9.0 (3.8)
(C) Patients with TS				
2006	7.4 (6.1)	6.7 (3.9)	7.9 (3.7)	10.6 (4.1)
2007	6.7 (4.1)	9.3 (3.3)	10.2 (4.0)	6.5 (3.0)
2008	13.5 (2.0)	8.5 (3.5)	8.8 (2.8)	12.1 (1.9)
2009	8.9 (3.4)	7.5 (3.7)	8.0 (4.6)	12.0 (2.2)
2010	9.0 (3.0)	8.6 (3.8)	6.7 (4.0)	6.2 (3.9)
2011	11.7 (2.2)	8.4 (3.2)	6.2 (3.1)	14.8 (2.3)
2012	7.6 (4.6)	7.7 (3.5)	8.7 (3.9)	8.6 (2.2)
2013	7.8 (3.8)	8.5 (4.1)	7.6 (3.3)	8.8 (3.2)
2014	8.8 (3.0)	7.8 (3.7)	10.9 (3.8)	8.6 (2.3)
2015	9.1 (3.4)	9.9 (4.3)	7.0 (2.5)	9.6 (4.6)
All	8.7 (3.7)	8.3 (3.7)	8.0 (3.8)	9.6 (3.7)

[a]Not applicable ($n = 1$). GHD, growth hormone deficiency; SGA, small for gestational age; SD, standard deviation; TS, Turner syndrome.

more than 40% of children started treatment late between 2013 and 2015.

The mean baseline doses in the different countries over the 10-year period (Table 3A) were mostly within the range of 25–35 µg/kg/day, as recommended in the Summary of Product Characteristics [18] and generally recommended in Europe. The mean (SD) baseline dose of GH for all years was higher in France (35.5 [7.3] µg/kg/day) and Switzerland (33.6 [8.6] µg/kg/day) than in the other countries analyzed (where the mean for all years ranged from 27.8–30.5 µg/kg/day; Table 3A). Although GH dose decreased statistically significantly over time in Germany ($p = 0.038$) (Supplemental Figure 1B), the decrease in actual mean dose was small – from 29.4 (7.4) to 27.8 (5.2) µg/kg/day – and, thus, of limited clinical relevance.

The mean height SDS values at baseline were below –2 SDS in all years in all countries, with a few exceptions (full data not shown). The mean (SD) height SDS values at baseline for the 10-year period overall ranged from –2.2 (1.5) (UK) to –2.6 (1.0) (Czech Republic). No statistically significant trends were observed over time except in Serbia and Montenegro, where in later years,

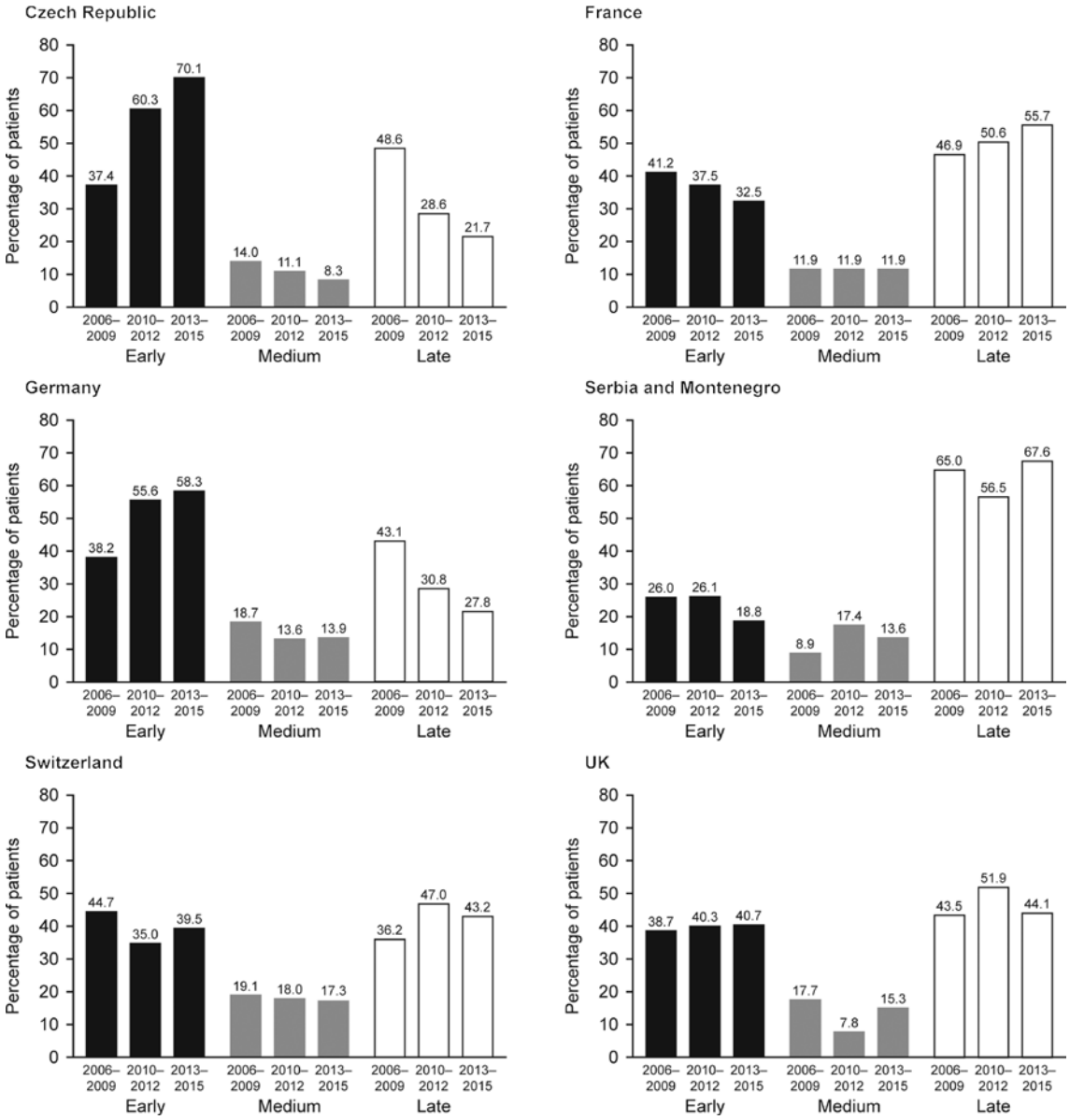

Figure 1: Distribution of patients with GHD by GH treatment start period (2006–2009, 2010–2012 or 2013–2015) and age group. Age groups were as follows: early: girls aged <8 years, boys aged <9 years; medium: girls aged 8–10 years, boys aged 9–11 years; and late: girls aged >10 years, boys aged >11 years. Distribution is shown as percentage of patients in each age group in the relevant period. GH, growth hormone; GHD, growth hormone deficiency.

Table 3: GH dose at treatment start in μg/kg/day, shown as mean (SD) for patients with GHD, short patients born SGA and patients with TS.

GH start year	Czech Republic	France	Germany	Serbia and Montenegro	Switzerland	UK
(A) Patients with GHD						
2006	33.0 (9.7)	35.3 (6.0)	29.4 (7.4)	30.6 (6.3)	32.3 (5.7)	30.3 (3.2)
2007	28.0 (7.1)	35.8 (8.3)	28.4 (7.1)	29.5 (4.7)	33.8 (10.0)	30.1 (6.0)
2008	29.5 (5.3)	36.0 (8.0)	27.5 (5.4)	29.4 (6.5)	36.3 (8.1)	29.6 (7.3)
2009	30.5 (5.7)	36.6 (8.4)	27.7 (6.0)	31.5 (6.0)	31.4 (9.5)	27.5 (5.1)
2010	30.0 (6.3)	35.9 (9.6)	27.4 (6.9)	30.5 (3.8)	33.3 (9.2)	30.2 (6.0)
2011	30.7 (5.3)	34.7 (6.8)	27.4 (4.6)	29.9 (4.7)	33.1 (8.1)	28.3 (5.5)
2012	28.0 (4.9)	35.3 (5.7)	27.3 (6.0)	32.2 (6.9)	35.2 (9.2)	28.5 (3.7)
2013	29.8 (5.0)	34.3 (5.2)	27.9 (5.5)	31.0 (6.4)	33.6 (7.9)	26.0 (5.0)
2014	30.8 (4.7)	36.3 (6.6)	26.5 (3.4)	29.6 (5.6)	33.7 (9.0)	27.0 (4.3)
2015	29.5 (4.9)	34.8 (5.4)	27.8 (5.2)	30.0 (4.3)	31.5 (5.9)	26.5 (4.2)
All	30.0 (5.7)	35.5 (7.3)	27.8 (6.1)	30.5 (5.7)	33.6 (8.6)	28.3 (5.5)

Year	Czech Republic	France	Germany	Serbia and Montenegro
(B) Short patients born SGA				
2006	38.5 (8.9)	44.7 (10.6)	34.6 (4.4)	65.4 (1.3)
2007	34.8 (6.7)	43.7 (11.8)	33.6 (5.3)	50.0 [a]
2008	33.4 (8.1)	41.6 (10.9)	33.0 (6.1)	40.3 (10.0)
2009	34.2 (4.8)	43.4 (10.5)	32.2 (6.3)	33.9 (9.7)
2010	39.2 (7.7)	44.3 (9.3)	34.2 (5.3)	32.9 (7.9)
2011	33.0 (5.6)	37.6 (6.5)	32.5 (6.8)	32.6 (7.7)
2012	36.0 (5.5)	40.2 (10.1)	30.0 (6.9)	32.7 (11.1)
2013	34.9 (3.2)	37.4 (6.6)	32.9 (5.1)	32.9 (7.6)
2014	34.1 (3.1)	41.0 (10.4)	31.4 (4.5)	30.7 (7.7)
2015	34.2 (2.8)	40.9 (9.1)	32.2 (4.5)	31.4 (5.6)
All	35.1 (6.1)	41.5 (9.9)	33.0 (5.7)	32.6 (8.6)
(C) Patients with TS				
2006	45.6 (3.7)	48.1 (8.9)	40.5 (10.7)	47.6 (7.3)
2007	49.1 (4.3)	49.2 (4.1)	41.5 (8.6)	44.1 (9.4)
2008	47.9 (4.9)	49.0 (4.0)	43.8 (10.2)	44.0 (13.7)
2009	43.5 (4.3)	47.5 (9.6)	42.6 (14.2)	45.4 (4.6)
2010	44.0 (7.4)	48.7 (10.7)	43.2 (9.5)	45.2 (5.0)
2011	45.2 (2.1)	45.7 (9.0)	38.5 (12.8)	44.5 (1.0)
2012	42.4 (6.7)	43.4 (10.7)	39.5 (10.7)	42.7 (6.2)
2013	42.3 (6.3)	45.5 (10.1)	37.3 (7.2)	43.5 (6.2)
2014	41.6 (4.2)	40.2 (9.8)	31.8 (10.1)	43.6 (6.1)
2015	43.7 (8.0)	45.6 (10.0)	36.5 (11.2)	39.8 (10.1)
All	44.1 (5.9)	46.3 (9.3)	40.0 (11.0)	44.4 (7.9)

[a]Not applicable (n = 1). GHD, growth hormone deficiency; SGA, small for gestational age; SD, standard deviation; TS, Turner syndrome.

patients were less growth retarded at diagnosis (Supplemental Figure 1C).

SGA

Proportions of female and male patients reported in each country fluctuated over time, but remained largely stable and were approximately equal (Table 1B).

The mean (SD) age at treatment start in patients born SGA for all years combined ranged from 6.9 (3.2) years (Czech Republic) to 9.0 (3.8) years (Serbia and Montenegro; Table 2B). From 2006 to 2015, the mean age decreased from 9.3 (3.6) to 5.9 (1.7) years in the Czech Republic ($p = 0.032$ for trend over time) and from 7.5 (3.2) to 6.1 (2.4) years in Germany ($p = 0.003$) (Table 2B and Supplemental Figure 2A). Over time, greater proportions of children started treatment early and lower proportions started treatment late in these two countries (Figure 2). Conversely, in France, mean age at treatment start increased from 7.5 (3.2) years in 2006 to 9.5 (3.7) years in 2015 – a statistically significant increase over time ($p = 0.003$), reflected in an increasing proportion of patients in the late treatment start group (Table 2B and

Figure 2). In both France and Serbia and Montenegro, over 40% of patients started treatment late between 2013 and 2015 (Figure 2).

The mean (SD) baseline dose of GH calculated for the 10-year period ranged from 32.6 (8.6) µg/kg/day (Serbia and Montenegro) to 41.5 (9.9) µg/kg/day (France; Table 3B). The baseline dose was generally higher in France than in the other countries. From 2006 to 2015, the actual mean dose decreased from 34.6 (4.4) to 32.2 (4.5) µg/kg/day in Germany ($p = 0.046$ for trend over time) (Table 3B and Supplemental Figure 2B). Similarly in France, the actual mean (SD) dose decreased from 44.7 (10.6) to 40.9 (9.1) µg/kg/day ($p = 0.045$). The mean dose decreased over time in Serbia and Montenegro, but patient numbers were low from 2006 to 2010 (Table 1B).

Children born SGA were very short at baseline, with mean height SDS values well below –2.5; this was observed over the whole period (full data not shown). The mean (SD) baseline height SDS values were between –2.6 (0.8) and –3.2 (0.9) in all years in all countries except Serbia and Montenegro, where they were generally between –2.0 (0.9) and –2.9 (1.4). In Germany between 2006 and 2015, a trend for shorter stature at diagnosis was observed ($p = 0.003$) (Supplemental Figure 2C). Conversely, in Serbia and Montenegro, children initiating GH treatment exhibited less growth retardation over time; again, patient numbers were very low from 2006 to 2010.

Turner syndrome

The mean (SD) age at baseline across all years for patients with TS was as follows: Czech Republic, 8.7 (3.7) years; France, 8.3 (3.7) years; Germany, 8.0 (3.8) years; and Serbia and Montenegro, 9.6 (3.7) years (Table 2C). No statistically significant trends in age at treatment start were observed (Supplemental Figure 3A). The distribution of patients by age at treatment start is shown in Figure 3;

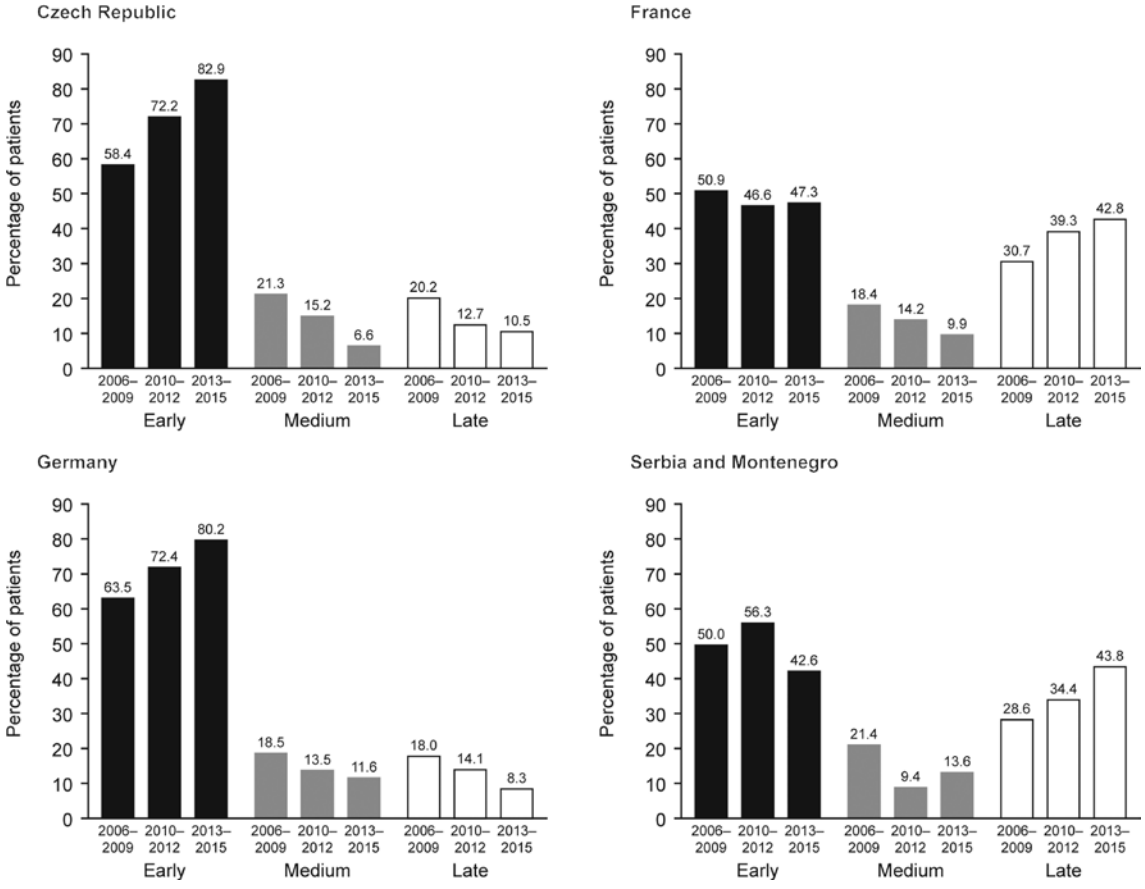

Figure 2: Distribution of short children born SGA by GH treatment start period (2006–2009, 2010–2012 or 2013–2015) and age group. Age groups were as follows: early: girls aged <8 years, boys aged <9 years; medium: girls aged 8–10 years, boys aged 9–11 years; and late: girls aged >10 years, boys aged >11 years. Distribution is shown as percentage of patients in each age group in the relevant period. GH, growth hormone; SGA, small for gestational age.

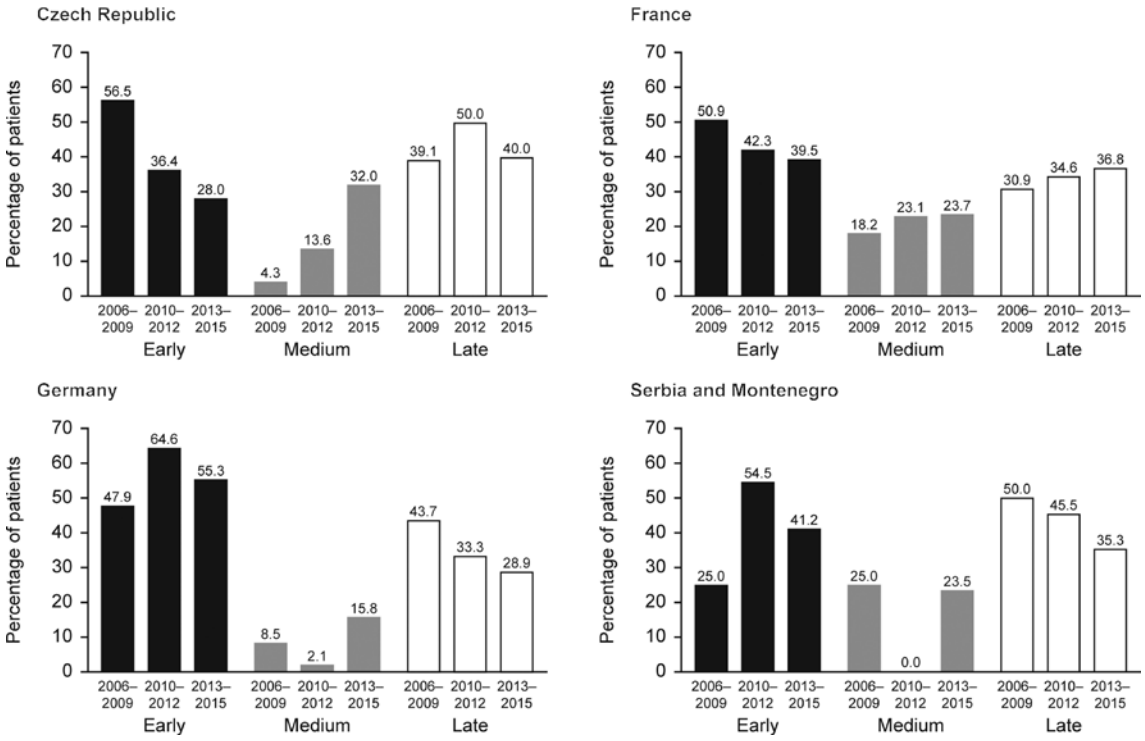

Figure 3: Distribution of patients with TS by GH treatment start period (2006–2009, 2010–2012 or 2013–2015) and age group. Age groups were as follows: early: girls aged <8 years, boys aged <9 years; medium: girls aged 8–10 years, boys aged 9–11 years; and late: girls aged >10 years, boys aged >11 years. Distribution is shown as percentage of patients in each age group in the relevant period. GH, growth hormone; TS, Turner syndrome.

patient numbers were too low to allow conclusions on patterns over time.

The mean (SD) baseline GH dose for all years ranged from 40.0 (11.0) µg/kg/day in Germany to 46.3 (9.3) µg/kg/day in France (Table 3C). Generally, the lowest mean doses were reported in Germany, ranging from 31.8 (10.1) to 43.8 (10.2) µg/kg/day, and the highest in France, ranging from 40.2 (9.8) to 49.2 (4.1) µg/kg/day. From 2006 to 2015, the actual mean dose decreased from 45.6 (3.7) to 43.7 (8.0) µg/kg/day in the Czech Republic ($p = 0.014$ for trend over time), from 48.1 (8.9) to 45.6 (10.0) µg/kg/day in France ($p = 0.016$), and from 40.5 (10.7) to 36.5 (11.2) µg/kg/day in Germany ($p = 0.013$) (Table 3C and Supplemental Figure 3B). These decreases were statistically significant and the mean doses were below the lowest recommended starting dose (45 µg/kg/day [18]) in all years in Germany, and in all years from 2012 to 2015 inclusive in the other countries, except for France.

The 10-year overall mean (SD) baseline height SDS values ranged from –2.3 (0.9) in France to –2.7 (1.0) in Serbia and Montenegro (full data not shown). Over time, height SDS decreased statistically significantly in France ($p = 0.033$), i.e. girls were becoming shorter at diagnosis (Supplemental Figure 3C).

Discussion

Analyses of data from NordiNet® IOS were undertaken to shed light on trends over time and differences in clinical practice between countries, with the aim of helping to optimize treatment, if clinical practice seems to diverge from treatment recommendations. The current analysis adds to the knowledge gained from a recent study of the KIGS® data [9] by examining different patient populations, and also supplements a recent report based on NordiNet® IOS [8] by analyzing the changes in baseline characteristics over time and by reporting proportions of patients by gender (GHD and SGA).

In the present study, girls generally made up a smaller proportion of patients treated for GHD than boys. The under-representation of girls treated for GHD has been reported previously [19, 20] and was also noted by Ranke and colleagues [9] for idiopathic GHD in their analysis of KIGS® data. This apparent gender bias may be due to under-referral of girls for short stature, or to over-referral of boys without organic causes of short stature [20]; alternatively, several studies have suggested that biological differences between the sexes may also contribute to the different number of boys and girls treated for short stature

[21–23]. Nevertheless, these findings emphasize the need for accurate growth monitoring during the healthcare maintenance of all children, particularly girls, to ensure appropriate referral and treatment.

An earlier age at treatment start has been shown to be associated with a better growth response among children with GHD [2], born SGA [4, 5] or with TS [6, 7]. A report from the ANSWER study showed significantly greater changes in height SDS during both years 1 and 2 of treatment of GHD for girls younger than 10 years compared with those 10 years or older and for boys younger than 11 years compared with those 11 years or older [24]. Significant differences between the two age groups were also shown for boys born SGA and for girls with TS [24]. Furthermore, a recent study demonstrated that early initiation of GH treatment in children with isolated GHD (girls aged <8 years, boys aged <9 years) improves their chance of achieving their genetic height potential [25]. The association between early treatment start and increased attainment of near-adult height and genetic potential in patients with GHD has also been shown in a study conducted in Sweden [3] and in studies confirming the importance of starting treatment before pubertal onset [26, 27].

In the present analysis, observed decreases over time in mean age at treatment start for GHD in the Czech Republic and Germany are relevant, as they mean that more children were prepubertal or in the early age group at treatment start. These changes were probably due to earlier detection of GHD, and in some cases to more precise diagnosis. However, large proportions of children with GHD still started treatment late in all countries between 2013 and 2015. Early detection of abnormal growth and referral to a pediatric endocrinologist, so that the underlying cause(s) can be identified, are critical for appropriate treatment. It is generally considered preferable that treatment with GH should start as soon as GHD has been diagnosed [28]. Aside from the evidence that age at treatment start is inversely associated with the response to therapy, starting GH replacement early also allows a longer duration of treatment and therefore more time for catch-up growth before children reach puberty, with the potential for better outcomes [29].

GH is indicated for use in short children born SGA who have failed to show catch-up growth by 4 years of age or later. The mean age at treatment start was well above 4 years in all the countries studied. The mean age decreased over time in the Czech Republic and Germany, but increased in France.

For TS, any interpretation of trends must be made with caution, as patient numbers were low. The mean age at treatment start ranged from 8.0 to 9.6 years between countries, with no clear patterns of change over time. Categorization by age group suggested large proportions of girls start treatment only after the age of 10 years. As with GHD and SGA, greater improvements in height gain have been associated with earlier treatment [7, 24, 30]. In line with earlier recommendations [31], many physicians start GH when the height of a girl who has been diagnosed with TS drops below the fifth percentile (approximately –1.645 SDS) on the growth chart, and in practice this has translated to an average starting age of 9 years [32, 33]. Recent guidelines from the International Turner Syndrome Consensus Group recommend initiating GH at around 4–6 years of age in children who have evidence of growth failure in the absence of other treatable causes, or who are already short or have a strong likelihood of short stature [34].

In models developed to identify the response to GH therapy, GH dose is a predictive variable for increase in height velocity in patients with GHD [2], born SGA [5] or with TS [6, 7]. The mean baseline doses for GHD in the different countries over the 10-year period were within the range of 25–35 μg/kg/day recommended in the Summary of Product Characteristics [18] and generally recommended in Europe. The observed slight decrease in dose over time in Germany might have been related to the younger age of the children at treatment start.

For patients born SGA, the baseline dose decreased over time in France and Germany, but remained close to or within the dose range recommended in an international consensus statement (35–70 μg/kg/day) [35]. In France, where patients born SGA were older at treatment start, the average GH doses were at the higher end of the label range. This may reflect differences between France and the other countries in the approved GH dose (upper dose, 50 μg/kg/day). The observed mean starting doses in France were smaller from 2011 onwards compared with preceding years. In 2010, the French Health Agency (AFSSAPS) issued an alert concerning GH treatment in childhood, referring to preliminary results from the French cohort of the European Union Safety and Appropriateness of GH treatments in Europe (EU SAGhE) study [36, 37]. However, a later position statement from an international GH safety workshop concluded that there was good available evidence in support of the use of recommended doses of GH in approved indications [38].

For patients with TS, the recommended dose range according to the Norditropin® Summary of Product Characteristics is between 45 and 67 μg/kg/day [18]. The recent guidelines recommend a starting dose of between 45 and 50 μg/kg/day in most cases, increasing to 68 μg/kg/day if needed [34]; in particular, higher doses may be considered in girls with a poor adult height prognosis. In a

study based on a database of all children receiving GH in Australia, Hughes and colleagues [39] concluded that the GH dose in the first year of treatment is a critical factor in determining the overall change in height SDS over the first 3 years of treatment. Importantly, a dose increment after the first year did not reverse the normal decline in the growth response. These authors suggested an age–dose interaction in patients with TS, highlighting the importance of both starting treatment at a young age and initiating treatment at a high dose. Furthermore, a study based on data from both NordiNet® IOS and ANSWER concluded that increase in height SDS was higher for patients with younger baseline age and higher GH dose, and that these findings support safe treatment optimization, including individualized GH dose titration consistent with approved product labels [40].

In the current analysis, the mean baseline doses for TS were low and were below 45 μg/kg/day in some years in all countries studied. The mean baseline dose also decreased significantly over time in the Czech Republic, France and Germany, decreasing in some cases to values even further below the recommended dose range. These low doses may reflect local conditions, such as an emphasis on safety. However, the evidence cited above indicates that starting below the recommended dosing range will not provide optimal results in the majority of patients.

The changes in height SDS values do not allow any conclusions to be drawn. The use of national references [12–17] to calculate the height SDS values may have contributed to the observed differences between countries, but was considered more appropriate than using a single reference. This conclusion was based on a recent study [41] that showed using updated national growth references may identify growth disorders with greater sensitivity than using international standards such as those produced by the World Health Organization [42, 43]. A limitation of our approach is the fact that some national references were more recent than others. However, our focus was on changes in height SDS over time in each country rather than differences in absolute values.

Other limitations of the present analyses are that only patients receiving treatment with Norditropin® and enrolled in NordiNet® IOS by the treating clinicians were included, which may represent a selection bias; that the comparisons across countries made here have not taken into account the variations in diagnostic criteria and the methods used, except where these are specifically discussed; that the mean values by country may also disguise different practices at treatment centers within each country; and that numbers in some countries were small for some indications and years.

Strengths of the study include the data validation at entry, as information is captured via a Good Clinical Practice-certified electronic platform, and the large number of enrolled patients in the GHD sub-cohort. This overview of trends over 10 years in real-life prescribing, without the limitations or time constraints associated with the short-term setting of a clinical trial, provides real-world evidence of the current and evolving practice of GH use.

Conclusions

This analysis of patients from six (GHD) or four (SGA, TS) countries showed trends that may indicate earlier diagnosis of and referral for these conditions from 2006 to 2015 in some countries. However, some aspects of real-life treatment practices still require increased awareness. For GHD, in four countries more than 40% of patients still started treatment late (i.e. aged >10 [girls] or 11 years [boys]) between 2013 and 2015, which may compromise their chances of achieving their genetic height potential. In general, more boys than girls with GHD were treated. Furthermore, the majority of patients with TS received GH doses below the lowest recommended dose. These results highlight the need for improved referral for treatment of children with short stature, and for dose optimization in patients with TS.

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